Asymmetric Transfer Hydrogenation of Imines

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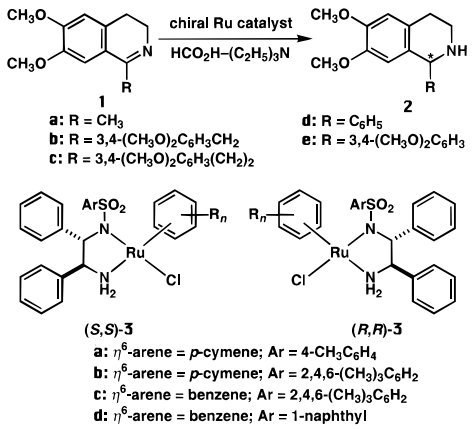
The cardinal significance of chiral amines in pharmaceutical and agrochemical substances demands the development of an efficient catalytic asymmetric reduction of imines. Certain imines were hydrogenated by chiral phosphine−Rh or −Ir catalysts with a substrate/catalyst molar ratio (S/C) of 100−1000 at 10−100 atm to give secondary amines in a fair to good ee[1] and by a chiral *ansa*-titanocene catalyst (S/C = 20, 6−140 atm) with 95−100% enantioselection.[2,3] Hydrosilylation with chiral phosphine−Rh complexes (S/C = 50−100)[4] or hydroboration with chiral oxazaborolidines (S/C = 10)[5,6] also effect the asymmetric reduction with 60−70% optical yield. These procedures, though viable, can still be improved for practical use in organic synthesis. Transfer hydrogenation using stable organic hydrogen donors is an attractive alternative in view of the less hazardous properties of the reducing agents and operational simplicity, as well as possible high overall cost performance. Although such reductions have emerged as a convenient method for asymmetric saturation of C=C[7] and C=O linkages,[8−12] its usage for enantioselective C=N reduction has remained totally undeveloped. Here we disclose for the first time that suitably designed chiral Ru(II) complexes catalyze efficiently the asymmetric reduction of imines with an inexpensive, well-behaving formic acid−triethylamine mixture under mild conditions.

In this investigation, we selected as the model reaction the reduction of the imine **1a** to salsolidine **2a** in the presence of Ru(II) catalysts **3**.[9−11,13] Screening experiments revealed that asymmetric reduction of **1a** was best effected with a 5:2 formic acid−triethylamine azeotropic mixture[14] in acetonitrile containing (*S*,*S*)-**3a** at 28 °C (S/C = 200, HCO_2H/**1a** = 6, [**1a**] = 0.5 M, 3 h), leading to (*R*)-**2a** in 95% ee and in >99% yield. The reaction was conducted equally well in various aprotic polar solvents including DMF, DMSO, and CH_2Cl_2, but not in ethereal or alcoholic media; the reaction in a neat formic acid−triethylamine mixture[11] was very slow.



The rate and enantioselectivity of the reaction are delicately influenced by the η^6-arene and 1,2-diamine ligands in **3**. The high efficiency attained with (*S*,*S*)-**3a** relies on not only the chirality of the N-tosylated 1,2-diamine but also the presence of the polar functional groups as well as the alkyl substituents on the *p*-cymene ligand. The NH_2 (not $N(CH_3)_2$) and $ArSO_2$ (not CF_3SO_2, C_6H_5CO, or CH_3CO) groups play crucial roles for the high reactivity, while the structure of the Ar group and the substitution pattern of the η^6-arene ligand may be fine-tuned depending on the imine substrates. The same result was obtained using the Ru complex **3** in situ formed from $[RuCl_2(\eta^6\text{-arene})]_2$ and the N-sulfonylated diamine in triethylamine without isolating the pure compound. The reaction was normally performed with an S/C ratio of 200, but the ratio could be as high as 1000.

Triethylamine is necessary; attempted reaction of **1a** with formic acid in acetonitrile containing **3a** failed to produce **2a**. Ru(II) complexes are known to catalyze the reversible process, $HCO_2H \rightleftharpoons H_2 + CO_2$,[15] and **3a** indeed catalyzes the decomposition of formic acid under the above described reaction conditions. However, the asymmetric reduction of the imine is a result of transfer hydrogenation by formic acid, and molecular hydrogen does not intervene. The reaction of **1a** in acetonitrile under a D_2 atmosphere (**1a**/(*S*,*S*)-**3a** = 200, D_2 60 atm, D_2:HCO_2H molar ratio = 24:1) under otherwise identical conditions gave (*R*)-**2a** in 93% ee and in >99% yield without deuterium incorporation at C(1) (^1H and ^2H NMR analysis).

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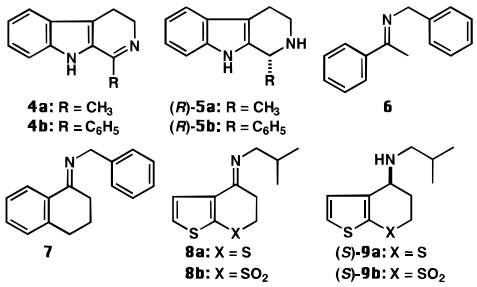
Table 1. Asymmetric Transfer Hydrogenation of Imines Catalyzed by Chiral Ru(II) Complexes[a]

					amine		
imine	catalyst	S/C	solvent	time, h	% yield[b]	% ee[c]	config[d]
1a	(*S*,*S*)-**3a**	200	CH_3CN	3	>99	95	*R*
1a[e]	(*S*,*S*)-**3a**	1000	CH_3CN	12	97	94	*R*
1b	(*R*,*R*)-**3b**	200	$(CH_3)_2NCHO$	7	90	95	*S*
1c	(*R*,*R*)-**3b**	200	CH_2Cl_2	12	99	92	*S*
1d	(*S*,*S*)-**3d**	200	CH_2Cl_2	8	99	84	*R*[f]
1e	(*R*,*R*)-**3d**	100	CH_2Cl_2	12	>99	84	*S*
4a	(*S*,*S*)-**3a**	200	$(CH_3)_2NCHO$	5	86	97	*R*
4a[e]	(*S*,*S*)-**3a**	1000	$(CH_3)_2NCHO$	12	89	93	*R*
4b	(*S*,*S*)-**3a**	200	$(CH_3)_2NCHO$	5	83	96	*R*[f]
6[g]	(*S*,*S*)-**3c**	200	CH_2Cl_2	36	72	77[h]	*S*
7	(*S*,*S*)-**3d**	100	CH_2Cl_2	6	90	89[i]	*S*[j]
8a	(*S*,*S*)-**3d**	100	CH_3CN	12	82	85	*S*[k]
8b	(*S*,*S*)-**3d**	100	CH_3CN	5	84	88	*S*

[a] A 5:2 formic acid−triethylamine azeotropic mixture (2.5 mL) was added to a solution of an imine (5 mmol) and a preformed Ru catalyst (0.02 mmol) in solvent (8 mL), and the mixture was stirred at 28 °C. [b] Isolated yield after flash chromatography on silica gel. [c] HPLC analysis using a Daicel Chiralcel OD column. [d] Determined by sign of the isolated product unless otherwise noted. [e] A 20 mmol scale reaction. [f] Determined by X-ray analysis of the (*S*)- or (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl derivative. [g] With a 3:2 formic acid−triethylamine mixture. [h] Sumichiral OA-4100. [i] Chiralcel OB column. [j] Determined after conversion to (*S*)-1,2,3,4-tetrahydro-1-naphthylamine. [k] Determined after oxidation to the sulfone.



Experiments using 2-propanol-*2-d* with formic acid or acetic acid in triethylamine revealed that 2-propanol cannot serve as a hydrogen source.

This catalytic method is particularly useful for the enantioselective reduction of cyclic imines to the amines with an ee value ranging from 90% to 97%, as illustrated in Table 1. Various substrates of type **1** with an alkyl, benzyl, or aryl substituent can be used, opening a new, general way to isoquinoline alkaloids.[16] N-methylation of (*S*)-**2b**, (*S*)-**2c**, and (*S*)-**2e** gives naturally occurring laudanosine, homolaudanosine, and cryptostyline II, respectively. Furthermore, this asymmetric reaction can be extended to the synthesis of optically active indoles **5** from **4**. Since most products are crystalline compounds, the enantiomeric purities are readily increased by recrystallization. Although the reaction of acyclic imines such as **6** (anti:syn = 94:6), **7**, and **8** is somewhat less stereoselective, this method allows a convenient preparation of the chiral amines, (*S*)-**9a** and (*S*)-**9b**, which serve as intermediates for the synthesis of MK-0417, a carbonic anhydrase inhibitor.[17]

The general sense of asymmetric induction with this catalytic system is schematically illustrated in Figure 1. In the stereodetermining hydrogen-transfer step, the chiral Ru species, probably a hydride, formally discriminates the enantiofaces at the sp^2 nitrogen atom of the cyclic and acyclic imine, generating a stereogenic sp^3 carbon (α control according to the latent trigonal center rule).[18] With acyclic imines, the difficulty in obtaining the geometrically pure compound as well as configurational instability,[2,19] causing syn−anti isomerization, tends to lower the extent of enantioselectivity.

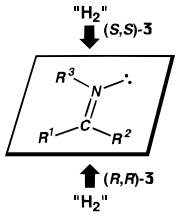


Figure 1. General sense of asymmetric transfer hydrogenation catalyzed by the Ru complex **3**.

Among the most notable feature of this reduction is the eminent functional group selectivity. Although the chiral Ru complex **3** does catalyze transfer hydrogenation of ketones in a formic acid−triethylamine mixture,[11] imines are more reactive under the present catalytic conditions. For example, the imine **1a** can be reduced *even in acetone* that contains (*S*,*S*)-**3a** (S/C = 200, [**1a**] = 0.5 M, **1a**:CH_3COCH_3 molar ratio = 1:5.4, 28 °C, 3 h) to give (*R*)-**2a** in >99% yield and in 95% ee accompanied with only 3% conversion of the solvent to 2-propanol. A competitive experiment using a 1:5 mixture of **1a** and structurally related 3,4-dimethoxyacetophenone in acetonitrile indicated that the ketimine is >1000 times more reactive than the ketone. The C=N/C=O chemoselectivity[1d] is superior to that observed in the stoichiometric reduction using $NaBH_3CN$ (98:1).[20] Simple olefinic substrates such as α-methylstyrene are inert to this reduction condition. The successful reaction with the 1-aryl derivatives **1d**, **1e**, and **4b** clearly excludes the possibility of the reaction pathway involving an imine−enamine isomerization.

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Supporting Information Available: Structural assignment of **8a** and **8b**, procedures for catalyst preparation and X-ray analysis of (*S*,*S*)-**3a**, experimental procedure of transfer hydrogenation and $[\alpha]_D$ values of the products, X-ray analyses of the (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl derivative of (*R*)-**2d** and the (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl derivative of (*R*)-**5b** (60 pages). Ordering information is given on any current masthead page.

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